TEXAS Health and Human Services

Dexmethylphenidate Hydrochloride Extended-Release

(Focalin XR®)

Classification:

Central Nervous System (CNS) Stimulant – Schedule CII

Pharmacology:

Mechanism of Action: Dexmethylphenidate hcl is the pharmacologically active *d-threo* enantiomer of racemic methylphenidate hcl (Ritalin®). Dexmethylphenidate hcl is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase release of these monoamines into the extraneuronal space.

Pharmacokinetics:

Absorption: Dexmethylphenidate produces a bi-modal plasma concentration-time profile that displays the first peak at approximately 1.5 hours (range 1-4 hours) and the second peak at approximately 6.5 hours (range 4.5-7 hours) after oral administration. The initial rate of absorption for dexmethylphenidate XR is similar to that of dexmethylphenidate IR tablets given in two doses 4 hours apart. Ranges vary more with dexmethylphenidate XR although the AUC after daily administration is equivalent to the same total dose of dexmethylphenidate IR. Due to first-pass metabolism, mean absolute bioavailability of dexmethylphenidate when administered in various formulations was 22-25%. No food effect study performed with dexmethylphenidate XR. However, food effect findings with racemic methylphenidate are applicable to dexmethylphenidate XR; after high fat breakfast, there was longer lag time until methylphenidate absorption began and variable delays in peak concentrations.

Distribution: Dexmethylphenidate has a volume of distribution of 2.65 ± 1.11 L/kg. The plasma protein binding of dexmethylphenidate is unknown. Although racemic methylphenidate is bound to plasma proteins by 12-15%. Plasma dexmethylphenidate concentrations decline

monophasically following oral administration of dexmethylphenidate XR.

Metabolism: Dexmethylphenidate is metabolized primarily to *d*-*a*-phenyl-piperidine acetic acid (*d*-ritalinic acid) by de-esterification. This metabolite has little to no pharmacological activity.

Elimination: The elimination half-life of dexmethylphenidate is variable with a mean of 3 hours (ranges 2-4.5 hours) with occasional elimination half-lives between 5-7 hours. Children have shorter elimination half-lives ranging from 2-3 hours.

Indications:

CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged 6 years and older.

Dosage:

Intended for oral administration once daily in the morning. Dexmethylphenidate XR may be given with or without food. For patients unable to swallow capsule, contents may be sprinkled on applesauce. Extended-release capsules should not be crushed, chewed, or divided.

Recommended starting dose for patients new to dexmethylphenidate XR is 5 mg once daily for pediatric population and 10 mg once daily for adults. The dose may be titrated up in 5mg increments for pediatric population and 10 mg increments for adults. Doses above 30 mg/day in children and 40 mg/day in adults have not been studied.

For patients currently using methylphenidate, initiate dexmethylphenidate XR with half the current daily dose of methylphenidate. For patients using dexmethylphenidate immediate release, switch to same daily dose of dexmethylphenidate XR.

Contraindications:

- Known hypersensitivity to methylphenidate, dexmethylphenidate or other product components
- Marked anxiety, tension, and/or agitation
- Glaucoma
- History of motor tics or a family history or diagnosis of Tourette's syndrome
- Structural cardiac abnormalities, cardiomyopathy, serious arrhythmias, or other serious cardiovascular problem

- During or within 14 days following discontinuation of a monoamine oxidase inhibitor (MAOI)

Warnings/Precautions:

- History of drug dependence or alcoholism – [Boxed Warning] may lead to tolerance and psychological dependence
- Pregnancy Category C – no adequately controlled studies in pregnant women
- Nursing Mothers – unknown if dexmethylphenidate is excreted in human milk
- Children under 6 years old – safety and efficacy of dexmethylphenidate XR not established
- Geriatric population – dexmethylphenidate XR has not been studied
- New onset or preexisting psychosis – stimulants may exacerbate symptoms
- New onset or preexisting bipolar disorder – possible induction of mixed/manic episode
- Seizure disorder – stimulants may lower seizure threshold
- Cardiac conditions (hypertension, heart failure, recent myocardial infarction, ventricular arrhythmia) – stimulants increase blood pressure and heart rate
- Visual disturbance – accommodation difficulty and blurry vision reported with stimulants
- Long-term suppression of growth in children
- Peripheral vasculopathy (including Raynaud's phenomenon)
- Priapism

Interactions:

- MAO inhibitors (concurrently or within previous 2 weeks)
- Use cautiously with pressor agents due to effects on blood pressure
- May decrease effectiveness of anti-hypertensives
- Antacids or acid suppressants could alter the release of dexmethylphenidate XR: can increase initial absorption but decrease delayed absorption since modified release is pH dependent
- Racemic methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, primidone), and tricyclic drugs (e.g. imipramine, clomipramine, desipramine); downward dose adjustments or therapeutic monitoring may be necessary.

Adverse Reactions:

The most common reasons for dexmethylphenidate XR discontinuation were motor and vocal tics, anorexia, insomnia and tachycardia in the pediatric population, and insomnia, anorexia, anxiety and feeling jittery in the adult population.

The most common side effects for pediatric patients were dyspepsia, decreased appetite, headache, and anxiety. Whereas the most common side effects for the adult population were dry mouth, dyspepsia, headache, and anxiety.

HHSC Cost: (daily dosing)

Dexmethylphenidate XR 5 mg: $3.95
Dexmethylphenidate XR 10 mg: $3.95
Dexmethylphenidate XR 15 mg: $2.97
Dexmethylphenidate XR 20 mg: $3.96
Dexmethylphenidate XR 25 mg: $3.26
Dexmethylphenidate XR 30 mg: $3.79
Dexmethylphenidate XR 35 mg: $3.26
Dexmethylphenidate XR 40 mg: $5.73

Price Comparison:
Dexmethylphenidate IR (BID dosing): 5 mg ($0.55), 10 mg ($0.70)
Concerta® (daily dosing): 18mg ($4.96), 27mg ($3.31), 36 mg ($5.48), 54 mg ($3.63)
Metadate CD® (daily dosing): 10mg ($2.56), 20 mg ($2.56), 30 mg ($2.56), 40 mg ($3.51), 50mg ($4.32), 60 mg ($4.32)

Monitoring:

HHSC monitoring: weight and height is all that is currently required
Drug labeling monitoring:

- Hematological monitoring: periodic CBC, differential, and platelet counts advised during prolonged therapy as there have been rare cases of leukopenia, anemia, and thrombocytopenic purpura.
- Blood pressure and heart rate: recommended for all patients due to risk for increase in blood pressure (2-4 mmHg) and heart rate (3-6 bpm).
- EKG: American Academy of Pediatrics does not recommend unless clinically indicated.

Product Identification:

Extended-Release Capsules:
5 mg (NDC 0078-0430-05) light-blue (imprinted NVR D5)

10 mg (NDC 0078-0431-05) light caramel (imprinted NVR D10)
15 mg (NDC 0078-0493-05) green (imprinted NVR D15)
20 mg (NDC 0078-0432-05) white (imprinted NVR D20)
25 mg (NDC 0078-0608-05) light-blue and white (imprinted NVR D25)
30 mg (NDC 0078-0433-05) light caramel and white (imprinted NVR D30)
35 mg (NDC 0078-0609-05) light-blue and light caramel (imprinted NVR D35)
40 mg (NDC 0078-0434-05) green and white (imprinted NVR D40)

Store Focalin XR® at 25°C (77°F), excursions permitted 15°–30°C (59°–86°F).
Dispense in tight container (USP).

Efficacy:

The effectiveness of dexmethylphenidate XR in the treatment of ADHD was established in multiple randomized, double-blinded, placebo-controlled studies in children, adolescents and adults who met DSM-IV criteria for ADHD.[1]

Children/Adolescents**:**

A double-blind, placebo-controlled study randomized 97 pediatric patients (ages 6-17) to receive dexmethylphenidate XR 5-30mg/day or placebo once daily for 7 weeks.[2] ADHD signs and symptoms were evaluated using teacher-rated Conners ADHD/DSM-IV Scales (CADS-T). The study compared mean change from baseline scores to endpoint scores using intent-to-treat analysis. Results showed statistically significant treatment effect in favor of dexmethylphenidate XR. Two additional cross-over studies in pediatric patients aged 6-12 years old compared dexmethylphenidate XR 20 mg to placebo. Dexmethylphenidate XR showed a statistically significant treatment effect vs. placebo on the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale combined score.[1]

An additional double blind, crossover study randomized 56 children and adolescents with ADHD to receive dexmethylphenidate XR (10, 20, 25-30 mg) or ER mixed amphetamine salts (10, 20, 25-30 mg).[3] Participants were enrolled in both trials with a week of placebo in between each drug period. Efficacy was assessed using ADHD Rating Scale-IV; adverse events measured with parent-completed Stimulant Side Effects Rating Scale. In the primary efficacy measure, results showed dexmethylphenidate ER and amphetamine ER were both associated with dose-dependent medication response in reductions in ADHD symptoms

regardless of stimulant class ($p<0.001$). Although side effect profile was similar in both stimulants and showed increase rates of insomnia and decreased appetite at higher doses, results were statistically insignificant.

Furthermore, two head-to-head, double-blind, crossover studies compared Focalin XR® to Concerta® (20 mg vs. 36 mg; 30 mg vs. 54 mg) in children aged 6-12 years.[4-5] Results demonstrated Focalin XR® had earlier onset of efficacy with greater improvements from baseline in SKAMP scores earlier in the day at 2 hours post dose, whereas Concerta® showed greater improvement and retained greater effect at 12 hours post dose. Differences in onset of action is likely attributed to different drug-release technology as d-MPH mimics twice-daily IR dosing and d,l-MPH ER formulation immediately releases 22% of drug, then gradually increases, peaking later in the day.

Adults:

The efficacy of Focalin XR® for the treatment of ADHD in adults (18-60 years old) was established in a 5-week multicenter, randomized, fixed-dose, double-blind, placebo-controlled study.[6] 221 adults were randomized to receive either 20 mg, 30 mg, or 40 mg of Focalin XR® or placebo once daily. Study drug participants were initiated on 10 mg/day and titrated by increments of 10 mg/day to randomly assigned fixed dose. ADHD signs and symptoms were evaluated by comparing mean change from baseline to endpoint using intention-to-treat analysis using DSM-IV ADHD Rating Scale. All three dexmethylphenidate XR groups had statistically significant improvements in mean ADHD RS-IV scores versus placebo with no definite increase in efficacy with increasing dose. A 6-month study follow up noted no clinically significant changes in vital signs, cardiac events, or any remarkable changes in laboratory data.[7]

Another study compared pharmacokinetics of dexmethylphenidate XR 20 mg given once daily, dexmethylphenidate IR 10 mg given 4 hours apart, and Ritalin LA 40 mg given once daily.[8] The primary pharmacokinetic endpoints (C_{max}, AUC) showed bioequivalence between all three formulations. Each formulation may offer advantages depending on time of day when ADHD symptoms occur. A systematic review evaluating long-acting methylphenidate formulations in the treatment of ADHD concluded past comparative data shows there is no formulation superior to another. Specific patient factors and subtle differences between formulations should be considered for treatment optimization.[9]

Conclusions:

The American Academy of Pediatrics recommends a stimulant, either a methylphenidate or amphetamine derivative, as first line therapy for ADHD.[10] MPH and AMP formulations have equal efficacy and similar side effect profiles according to several review, practice guidelines, and algorithms.[3] The choice of formulation depends on patient-specific factors such as patient age, preferred length of coverage time, ability to swallow tablets/capsules, expense of medication, time of day when ADHD symptoms occur, and abuse potential. If a trial with one group of stimulants is unsuccessful, a trial from the second group should be attempted. Although more expensive, extended-release formulations are generally preferred over immediate-release formulations due to their longer duration of action and dosing convenience. Unlike immediate-release formulations, they preclude the need for school-based administration. Some adolescents may need coverage for more than 12 hours, requiring the need for an immediate-release formulation in addition to an extended-release formulation. For patients unable to swallow tablets/capsules, long-acting capsules containing microbeads may be opened and sprinkled on food. Other formulation alternatives include a chewable tablet, long-acting suspension, long-acting orally disintegrating tablet, or transdermal patch. If time of ADHD symptoms occur later in the day, patients may benefit from long acting coverage such as Concerta® that peaks less in the morning with an increased effect later in the day. Dexmethylphenidate XR has biphasic peaks and a duration of 8-12 hours, which may benefit patients who have ADHD symptoms throughout the entire school day. In regards to efficacy of stimulants, dexmethylphenidate has similar efficacy compared to other methylphenidate and amphetamine formulations. In conclusion, it would be beneficial to add dexmethylphenidate XR to our formulary. It is the only other stimulant that is not on our formulary and would benefit patients that come into our facility already on dexmethylphenidate XR. It is now available in generic and comparable in price to other stimulants. In addition, it would be advantageous to have in our formulary should a drug-shortage on other stimulants arise.

Recommendation:

Recommended for addition to the formulary

References:

1. Product Information: FOCALIN XR(TM) extended-release oral capsules, dexmethylphenidate hydrochloride extended-release oral capsules.

Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2015. –revised 1/2017
2. Greenhill L, Muniz R, Ball R, Leving A, Pestreich L, and Jiang H. Efficacy and safety of dexmethylphenidate extended-release capsules in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006;45(7):817-823.
3. Stein MA, Waldman ID, Charney E, Aryal S, Sable C, Gruber R, and Newcorn JH. Dose Effects and Comparative Effectiveness of Extended Release Dexmethylphenidate and Mixed Amphetamine Salts. *Journal of Child and Adolescent Psychopharmacology*. 2011; *21*(6): 581–588.
4. Muniz R, Brams M, Mao A, McCague K, Pestreich L, and Silva R. Efficacy and safety of extended-release dexmethylphenidate compared with d,l-methylphenidate and placebo in the treatment of children with attention-deficit/hyperactivity disorder: a 12-hour laboratory classroom study. *Journal Of Child And Adolescent Psychopharmacology*. 2008; *18*(3), 248-256.
5. Silva R, Muniz R, McCague K, Childress A, Brams M, and Mao A. Treatment of children with attention-deficit/hyperactivity disorder: results of a randomized, multicenter, double-blind, crossover study of extended-release dexmethylphenidate and D,L-methylphenidate and placebo in a laboratory classroom setting. *Psychopharmacology Bull.* 2008; 41(1), 19-33.
6. Spencer TJ, Adler LA, McGough JJ, Muniz R, Jiang H, Pestreich, L. and the Adult ADHD Research Group. Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2007; 61(12):1380-7.
7. Adler L A, Spencer T, McGough JJ, Jiang H, Muniz R. Long-term effectiveness and safety of dexmethylphenidate extended-release capsules in adult ADHD. *J Atten Disord. 2009; 12(5):449-59.*
8. Tuerck D, Wang Y, Maboudian M, Wang Y, Sedek G, Pommier F, Appel-Dingemanse S. Similar bioavailability of dexmethylphenidate extended (bimodal) release, dexmethylphenidate immediate release and racemic methylphenidate extended (bimodal) release formulations in man. *Int J Clin Pharmacol Ther*. 2007; 45:662–668.
9. Coghil D, Banaschewski T, Zuddas A, Pelaz A, Gagliano A, Doepfner M. Long-acting methylphenidate formulations in the treatment of attention-deficit/hyperactivity disorder: a systematic review of head-to-head studies. *BMC Psychiatry*. 2013; 13: 237.
10. American Academy of Pediatrics. Implementing the Key Action Statements: An Algorithm and Explanation for Process of Care for the Evaluation, Diagnosis, Treatment, and Monitoring of ADHD in Children and Adolescents. *American Academy of Pediatrics*. 2011; 128(5): SI1-121.

Prepared by:

Kassandra Cervera, Pharm.D. Student Intern
Austin State Hospital
September 2018

Reviewed by:

Lisa M. Mican, Pharm.D., BCPP
Austin State Hospital
Clinical Pharmacist
September 2018